Welcome to the CTTI ABDD Pediatric Trials Project Recommendations Presentation

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Recommendations for addressing scientific and operational challenges in pediatric clinical trials for antibacterial drugs

Sumathi Nambiar, FDA
John Bradley, UCSD
Gary Noel, Johnson & Johnson

February 16, 2017
Agenda

- Introduction to CTTI and CTTI’s ABDD program
  - Pamela Tenaerts, CTTI
- Introduction to the Pediatric Trials project
  - Sumathi Nambiar, FDA
- Project Recommendations
  - John Bradley, UCSD
- Project Recommendations
  - Gary Noel, Johnson & Johnson
- Next Steps and Moderated Discussion
  - Pamela Tenaerts, CTTI
Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.
CTTI Strengths

Public-Private Partnership
co-founded by Duke University & FDA
involves all stakeholders
90 members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials
CTTI Strategic Plan

MISSION STATEMENT
To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

GOALS
Create recs & tools | Make data publicly available | Communicate broadly | Demonstrate impact | Characterize clinical trial landscape

AREAS OF STRATEGIC FOCUS
Systematic evidence generation | Patients as equal partners | Clinical trials designed with a focus on quality & efficiency | Trials addressing emerging public health concerns | Safe & ethical trials that are streamlined
2016 CTTI Membership

*These numbers reflect organizations on CTTI’s Steering Committee (SC). Industry includes 4 biotech, 3 CRO, 3 device/diagnostic, 11 pharma, and 2 technology. In addition, the SC includes 3 individual patient/caregiver representatives.
CTTI Methodology

1. State Problem
   - Issue Statement, Project Plan

2. Gather Evidence
   - Literature Reviews, Multi-stakeholder Meetings, Surveys, Interviews

3. Find Solution
   - Team Meetings, Multi-stakeholder Meetings

4. Refine Ideas
   - Team Meetings, Multi-stakeholder Meetings

5. Action
   - Workshops, Pilot Studies, Measure Impact

Steps:
- Identify Research Impediments
- Identify Gaps/Barriers
- Analyze and Interpret Findings
- Develop Recommendations/Tools
- Disseminate & Drive Adoption
Evidence guides the journey to solutions

We use quantitative & qualitative research methods, selecting those best aligned with each project’s objectives, to:

- Identify/describe “what is going on” to gain a better understanding of a particular phenomenon
- Move beyond individual views to a more complete and objective understanding of the disincentives and motivators for change

Equipped with data, we then challenge assumptions, identify roadblocks, build tools and develop recommendations to change the way people think about and conduct clinical trials.
CTTI Recommendations & Tools

- Streamline **HABP/VABP Trials**
- Organize **DMCs** to ensure accumulating data do not suggest undue harm to patients
- Move **Recruitment** planning upstream to reduce barriers to participation: Create Recruitable protocols
- Develop a better **IND Safety Reporting** system (3)
- Perform higher quality **Informed Consent** process
- Involve **Patient Groups** as equal partners in Clinical Trials: Engage Early, Engage Often
- Apply **Quality by Design (QbD)** principles to create better protocols: Just think!
- Improve ethics review process via use of **Central IRB** (2)
- Reduce inefficiencies of investigator **GCP Training**
<table>
<thead>
<tr>
<th>Complete Projects</th>
<th>Systematic Evidence Generation</th>
<th>Patients as Equal Partners</th>
<th>Efficient &amp; Quality Trials</th>
<th>Public Health Concern</th>
<th>Safe &amp; Ethical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Large Simple Trials</td>
<td>GCP Training</td>
<td>ABDD Streamlining</td>
<td>Central IRB</td>
<td></td>
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<td></td>
<td></td>
<td>Monitoring</td>
<td>HABP/VABP Trials</td>
<td>Central IRB Advancement</td>
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<td>Quality by Design</td>
<td>ABDD Unmet Need</td>
<td>DMCs</td>
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<td></td>
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<td>Recruitment</td>
<td>Long-Term Opioid Data</td>
<td>Informed Consent</td>
<td></td>
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<td>Site Metrics</td>
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<td>IND Safety</td>
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<td>SAE Reporting</td>
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<td>Active Projects</td>
<td>MCT Legal &amp; Regulatory</td>
<td>Patient Groups &amp; Clinical Trials</td>
<td>GCP Follow On Investigator Turnover</td>
<td>ABDD HABP/VABP Studies</td>
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<td>MCT Mobile Devices</td>
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<td>IND Safety Advancement</td>
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<td>MCT Novel Endpoints</td>
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<td>Pregnancy Testing</td>
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<td>MCT Stakeholder Perceptions</td>
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<td>Real World Evidence</td>
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<td>Registry Trials</td>
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CTTI ABDD Program & Projects

9/2012 – FDA Engaged CTTI in ABDD

9/2014 – New CTTI R18 grant included demonstration studies

PROJECTS:
- Streamlining HABP/VABP Trials
- Pediatric Trials
- Unmet Need

- Protocol Elements
- Data Collection
- Site Networks
- Use & Acceptance of Streamlined Development
- Statistical Issues
- HABP/VABP Risk Factor Study
- HABP/VABP Early Enrollment Pilot Study
Why did we do the ABDD Peds project?

Annual Adult (2007-10)
Peds ID (2008-15)
ID Trials

- Adult ID Trials (n=avg 529/yr)
- Peds ID Trials
# Project Team

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<tr>
<th>Name</th>
<th>Affiliation</th>
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<tr>
<td>Daniel Benjamin</td>
<td>Duke University</td>
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<tr>
<td>Sumathi Nambiar</td>
<td>Food and Drug Administration</td>
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<tr>
<td>Gary Noel</td>
<td>Johnson and Johnson</td>
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<tr>
<td>Kunyi Wu</td>
<td>Food and Drug Administration</td>
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<tr>
<td>John Bradley</td>
<td>University of California, San Diego</td>
</tr>
<tr>
<td>John Farley</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>Breck Gamel</td>
<td>Individual Patient/Caregiver</td>
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<tr>
<td>Ethan Hausman</td>
<td>Food and Drug Administration</td>
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<tr>
<td>Hasan Jafri</td>
<td>Medimmune</td>
</tr>
<tr>
<td>Brian Smith</td>
<td>Duke University</td>
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<tr>
<td>Edward Spindler</td>
<td>The Medicines Company</td>
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<tr>
<td>Pamela Tenaerts</td>
<td>Clinical Trials Transformation Initiative</td>
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<tr>
<td>Rose Tiernan</td>
<td>Food and Drug Administration</td>
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<td>Chris Wheeler</td>
<td>Food and Drug Administration</td>
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<tr>
<td>Jamie Roberts</td>
<td>CTTI Project Manager (former)</td>
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<tr>
<td>Annemarie Forrest</td>
<td>CTTI Project Manager (current)</td>
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<tr>
<td>Amy Corneli</td>
<td>CTTI Social Science Lead</td>
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Introduction to the CTTI ABDD Pediatric Trials Project

Sumathi Nambiar
Pediatric Product Development

- **Pediatric Research Equity Act (PREA)**
  - Requires companies to assess safety and effectiveness of certain products in pediatric patients

- **Best Pharmaceuticals for Children Act (BPCA)**
  - Provides a financial incentive to companies to voluntarily conduct pediatric studies
Pediatric Product Development

Pediatric product development is held to the same evidentiary standard as adult product development.

Approaches to support the safe and effective use of drugs in pediatric populations:

- Adequate and well-controlled investigations of a specific pediatric indication different from the indication(s) approved for adults.
- Evidence from adequate and well-controlled investigations in pediatric populations to support the same indication(s) approved for adults.
- Evidence from adequate and well-controlled studies in adults and additional information in the specific pediatric population.
Pediatric Antibacterial Drug Development

- For most adult indications, efficacy can be extrapolated to the pediatric population as the course of disease and the effect of the drug are sufficiently similar in adults and pediatric patient population (21 CFR 314.55)
- Dosing cannot be fully extrapolated
- Safety cannot be fully extrapolated
Pediatric Antibacterial Drug Trials

- The time lag between approval of an anti-infective drug in adults and approval in children is very long (> 5 years); pediatric use information rarely includes information regarding use of the product in neonates.
- Over the last several years, the Agency has streamlined some aspects of pediatric antibacterial drug trials.
- There is a critical need to assess the challenges and find solutions so that safe and effective therapies are available for children.
Project Overview

**Purpose**
- Address the scientific and operational challenges in the design, conduct and quality of pediatric antibacterial drug trials

**Anticipated Impact**
- Improved feasibility, design and conduct of pediatric antibacterial drug trials
Findings

- A review of the Aggregate Analysis of ClinicalTrials.gov (AACT) database from 2008-2015 showed that there were very few trials of systemic anti-infective drugs in children (105 trials; <1% of all pediatric trials registered); 30% of the trials enrolled neonates.
- The informed consent process needs to be improved.
- There are opportunities to streamline pediatric antibacterial drug trials.
- There is a need for greater engagement among stakeholders.
Project Recommendations

John Bradley
Global Collaborations

Establish global collaborations, networks and master protocols to expedite the availability of evidence regarding the safety and efficacy of antibacterial drugs in children.

- Leverage pathways for drug development (clinical trial design for outcomes/endpoints) to achieve consistency and alignment between regulatory agencies in the US, the EU and other global partners (already underway between FDA and EMA)
- Develop master clinical trial protocols to conduct pediatric antibacterial drug trials across the globe
- Develop global networks of engaged, accountable, productive clinical sites.
Pediatric Drug Development Planning

- Sponsors should engage regulatory agencies (eg, FDA and EMA) as early in drug development as possible.
- Initiate clinically essential, required pediatric studies at the earliest time that is safe and practical.
- Some studies in children will not reflect adult indications (neonatal sepsis, osteomyelitis), and may require an innovative approach to trial design.
Protocol Design and Development

Minimize the burden of participation for patients, their caregivers and study sites.

- Obtain the input of stakeholders who will be affected by implementation of the trial.
- Identify barriers that will affect trial efficiency and enrollment, such as visit windows (days of evaluation for outcomes, especially return visits to hospital), invasive testing (venipuncture), etc.
- Fund studies for participation of clinical research sites consistently for the real costs for the sites.
- Streamline data collection for regulators and sponsors to include only that which is relevant to the goals of the trial.
Protocol Design and Development

- Broaden the eligibility criteria to be as inclusive as possible to achieve the trial’s scientific goals and minimize the risks to participating children.

  There is no “perfect” study patient with perfect organ function and no associated illness that might make it harder to identify a drug-attributable side effect.

  Consider simultaneous enrollment of all age groups above 2 years of age for phase 1 single dose protocols (when appropriate).

- Improve consistency and standardization of adverse event reporting to allow better assessment of study drug-attributable toxicity.
Special Considerations for Trials in Neonates

Take special care when planning studies with neonates for obtaining critical safety and drug exposure information for all stages of neonatal development.

- Using minimal sampling of blood or plasma
- Conduct opportunistic sampling (e.g., if a baby is going to have blood drawn for another test, is there sufficient blood left over to run the antibiotic assay?)
- Spinal fluid studies from a subset of neonates on protocols, as neonates still get meningitis and we need to know how much antibiotic gets into spinal fluid
Project Recommendations

Gary Noel
Informed Consent

Recognize and address the challenges of obtaining consent of children and their families

- Follow best practices related to informed consent for
  - Who: approaches a parent or caregiver
  - When: to approach a parent or caregiver
  - How: to approach a parent or caregiver
Informed Consent

Use an informed consent process that empowers families and provides the information needed for families to understand the trial and make the best decision for their child.

- Support the training and development of experienced family or peer navigators to guide inexperienced families and children through the clinical trial process.
- With the assistance of family or peer navigators and other stakeholders, develop a list of FAQs about the study and participation.
- Consider electronic informed consent.
- Always use lay language.
Engaging Healthcare Providers

Provide education and support for healthcare providers that improves their understanding of the importance of involving children in antibacterial clinical trials.

- Determine the best mechanisms for educating healthcare providers about the value of new antibacterial drugs and the need for pediatric clinical trials.
- Establish trusting relationships with referring healthcare providers.
- Provide adequate support for healthcare providers who wish to become investigators.
Pediatric Labeling

Engage all stakeholders in continuing discussion of labeling antibacterial drugs for use in children.

- Educational efforts are needed to ensure that healthcare providers and parents understand how to read, interpret, and find specific pediatric information in drug labeling.

- Recognize the importance of expedited pediatric labeling of antibacterials as soon as possible after their approval in adults to ensure appropriate use in children and infants.
Reporting Trial Results

Report pediatric trial results so that these data are available to health care providers and the public.

- Report in ClinicalTrials.gov.
- Submit manuscripts.
- Present results at major meetings and conferences.
What’s next?

Pamela Tenaerts
Associated CTTI Recommendations

- Principles and Recommendations for Quality by Design
- Best Practices for Patient Group Engagement Around Clinical Trials
- Recommendations for Informed Consent
- Recommendations for Strategic Recruitment Planning
- Recommendations for IND Safety Assessment and Communication

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Disseminating recommendations

- Preparing evidence and recommendations for publication
- Preparing abstracts for professional meeting presentations
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- Follow us on Twitter, Facebook, and LinkedIn, and sign up to receive CTTI email alerts
Driving adoption of recommendations

- How can you make these recommendations actionable in your organization?
- Who in your organization is uniquely positioned to leverage these recommendations?
- What additional actions can CTTI take to facilitate adoption of these recommendations?
Thank you.

Annemarie Forrest
Annemarie.forrest@duke.edu
919-943-0358